CLINICAL PHARMACOKINETICS

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USES OF PHARMACOKINETICS

- BASIC STUDIES OF BIODISTRIBUTION (PET SCAN)
- DEVELOPMENT AND EVALUATION OF NEW DRUGS
- BASIS FOR PRESCRIBING DRUG DOSAGE

TARGET CONCENTRATON STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

⇩

BEGIN THERAPY

⇩

ASSESS THERAPY
PATIENT RESPONSE
DRUG LEVEL

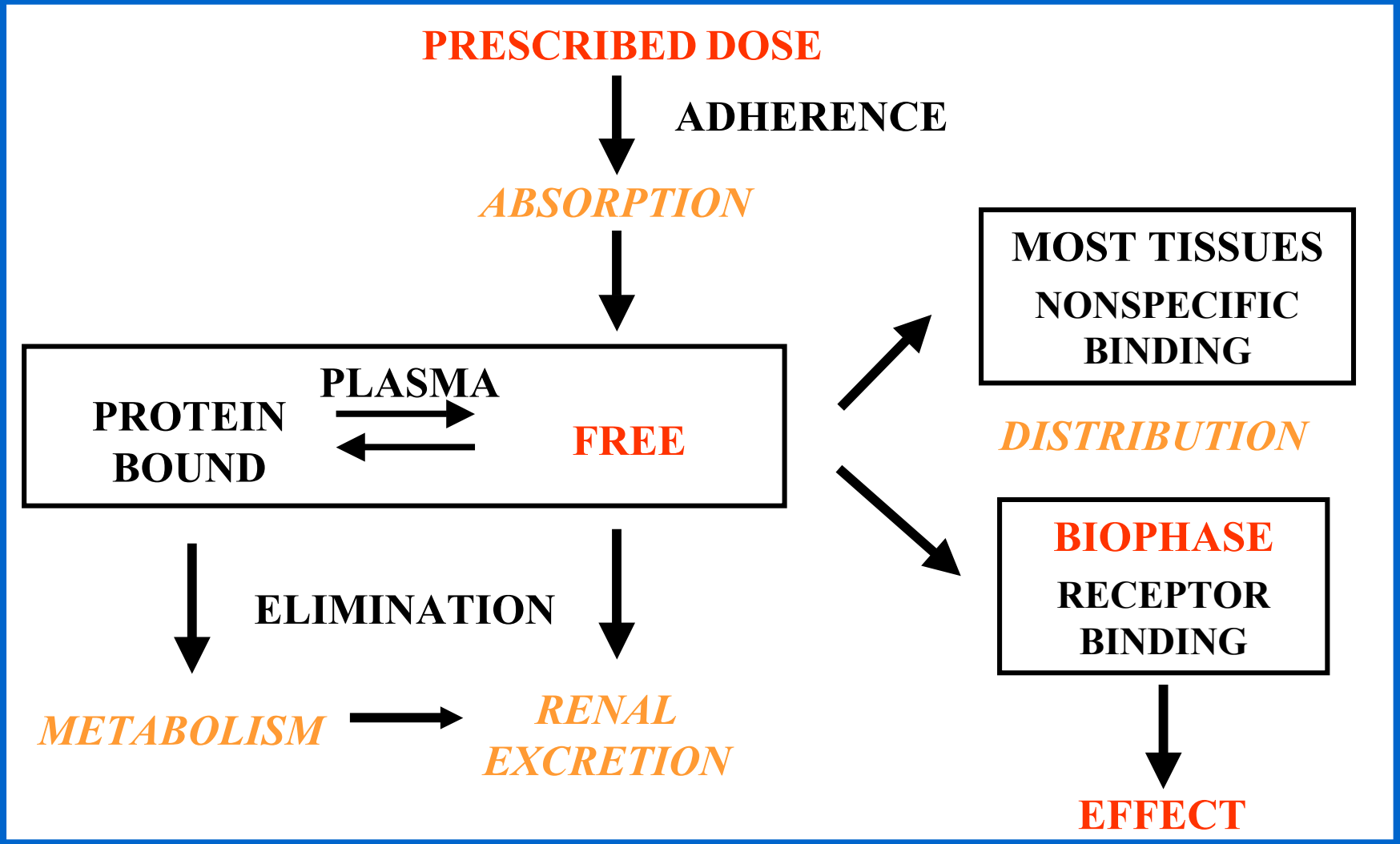
⇩

REFINE DOSE ESTIMATE

⇩

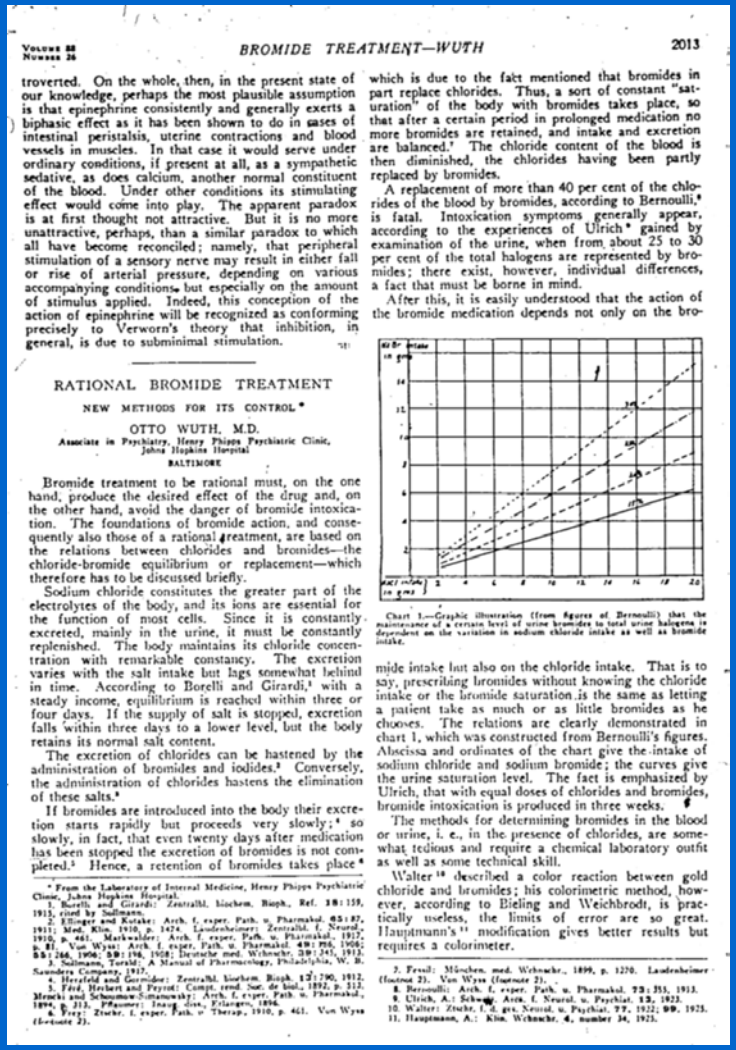
ADJUST DOSE

RATIONALE FOR PLASMA LEVEL MONITORING



FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

Wuth O. JAMA 1927;88:2013-17.



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BROMIDE TREATMENT—WUTH

2013

troverted. On the whole, then, in the present state of our knowledge, perhaps the most plausible assumption is that epinephrine consistently and generally exerts a biphasic effect as it has been shown to do in cases of intestinal peristalsis, uterine contractions and blood vessels in muscles. In that case it would serve under ordinary conditions, if present at all, as a sympathetic sedative, as does calcium, another normal constituent of the blood. Under other conditions its stimulating effect would come into play. The apparent paradox is at first thought not attractive. But it is no more unattractive, perhaps, than a similar paradox to which all have become reconciled; namely, that peripheral stimulation of a sensory nerve may result in either fall or rise of arterial pressure, depending on various accompanying conditions, but especially on the amount of stimulus applied. Indeed, this conception of the action of epinephrine will be recognized as conforming precisely to Verworn's theory that inhibition, in general, is due to subminimal stimulation.

RATIONAL BROMIDE TREATMENT

NEW METHODS FOR ITS CONTROL *

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Bromide treatment to be rational must, on the one hand, produce the desired effect of the drug and, on the other hand, avoid the danger of bromide intoxication. The foundations of bromide action, and consequently also those of a rational treatment, are based on the relations between chlorides and bromides—the chloride-bromide equilibrium or replacement—which therefore has to be discussed briefly.

Sodium chloride constitutes the greater part of the electrolytes of the body, and its ions are essential for the function of most cells. Since it is constantly excreted, mainly in the urine, it must be constantly replenished. The body maintains its chloride concentration with remarkable constancy. The excretion varies with the salt intake but lags somewhat behind in time. According to Borelli and Girardi,[1] with a steady income, equilibrium is reached within three or four days. If the supply of salt is stopped, excretion falls within three days to a lower level, but the body retains its normal salt content.

The excretion of chlorides can be hastened by the administration of bromides and iodides.[2] Conversely, the administration of chlorides hastens the elimination of these salts.[3]

If bromides are introduced into the body their excretion starts rapidly but proceeds very slowly;[4] so slowly, in fact, that even twenty days after medication has been stopped the excretion of bromides is not completed.[5] Hence, a retention of bromides takes place[6] which is due to the fact mentioned that bromides in part replace chlorides. Thus, a sort of constant "saturation" of the body with bromides takes place, so that after a certain period in prolonged medication no more bromides are retained, and intake and excretion are balanced.[7] The chloride content of the blood is then diminished, the chlorides having been partly replaced by bromides.

A replacement of more than 40 per cent of the chlorides of the blood by bromides, according to Bernoulli,[8] is fatal. Intoxication symptoms generally appear, according to the experiences of Ulrich[9] gained by examination of the urine, when from about 25 to 30 per cent of the total halogens are represented by bromides; there exist, however, individual differences, a fact that must be borne in mind.

After this, it is easily understood that the action of the bromide medication depends not only on the bromide intake but also on the chloride intake. That is to say, prescribing bromides without knowing the chloride intake or the bromide saturation is the same as letting a patient take as much or as little bromides as he chooses. The relations are clearly demonstrated in chart 1, which was constructed from Bernoulli's figures. Abscissa and ordinates of the chart give the intake of sodium chloride and sodium bromide; the curves give the urine saturation level. The fact is emphasized by Ulrich, that with equal doses of chlorides and bromides, bromide intoxication is produced in three weeks.

Chart 1.—Graphic illustration (from figures of Bernoulli) that the maintenance of a certain level of urine bromides in total urine halogens is dependent on the variation in sodium chloride intake as well as bromide intake.

The methods for determining bromides in the blood or urine, i. e., in the presence of chlorides, are somewhat tedious and require a chemical laboratory outfit as well as some technical skill.

Walter[10] described a color reaction between gold chloride and bromides; his colorimetric method, however, according to Bieling and Weichbrodt, is practically useless, the limits of error are so great. Hauptmann's[11] modification gives better results but requires a colorimeter.

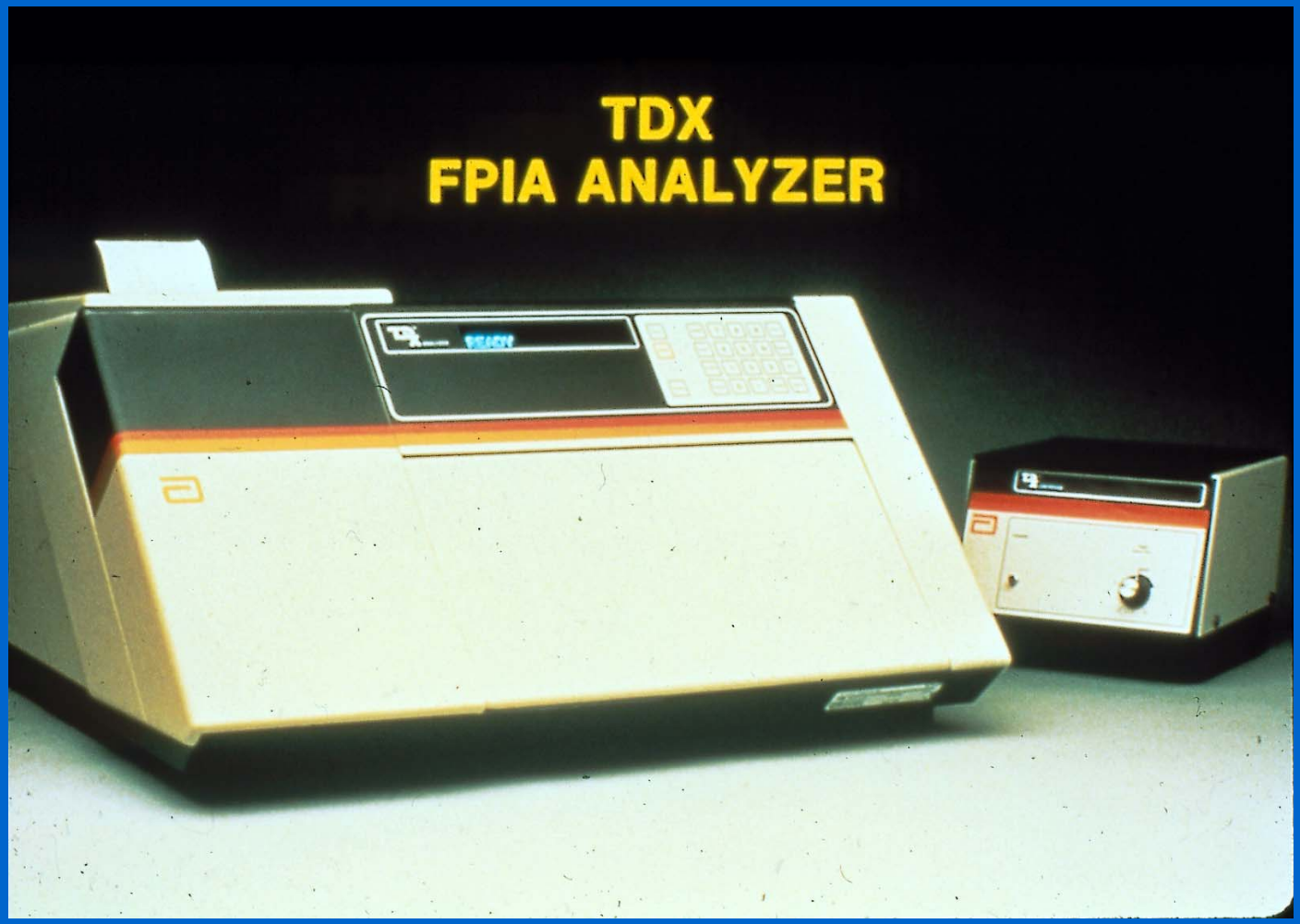
* From the Laboratory of Internal Medicine, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital.

1. Borelli and Girardi: Zentralbl. biochem. Biophy., Ref. 18: 159, 1913, cited by Sollmann.
2. Ellinger and Kotake: Arch. f. exper. Path. u. Pharmakol. 65: 87, 1911; Med. Klin. 1910, p. 1424. Lindenheimer: Zentralbl. f. Neurol., 1910, p. 461. Markwalder: Arch. f. exper. Path. u. Pharmakol., 1917, p. 81. Von Wyss: Arch. f. exper. Path. u. Pharmakol. 49: 196, 1906; 55: 266, 1906; 59: 198, 1908; Deutsche med. Wchnschr. 39: 345, 1913.
3. Sollmann, Torald: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1917.
4. Herzfeld and Gerrider: Zentralbl. biochem. Biophy. 12: 290, 1912.
5. Féré, Herbert and Feyrot: Compt. rend. Soc. de biol., 1892, p. 512. Mencki and Schoumow-Simanowsky: Arch. f. exper. Path. u. Pharmakol., 1894, p. 313. Pflaumer: Inaug. diss., Erlangen, 1896.
6. Frey: Ztschr. f. exper. Path. u. Therap., 1910, p. 461. Von Wyss (footnote 2).
7. Freud: München. med. Wchnschr., 1899, p. 1270. Laudenheimer (footnote 2). Von Wyss (footnote 2).
8. Bernoulli: Arch. f. exper. Path. u. Pharmakol. 73: 353, 1913.
9. Ulrich, A.: Schweiz. Arch. f. Neurol. u. Psychiat. 13, 1923.
10. Walter: Ztschr. f. d. ges. Neurol. u. Psychiat. 77, 1922; 99, 1925.
11. Hauptmann, A.: Klin. Wchnschr. 4, number 34, 1925.

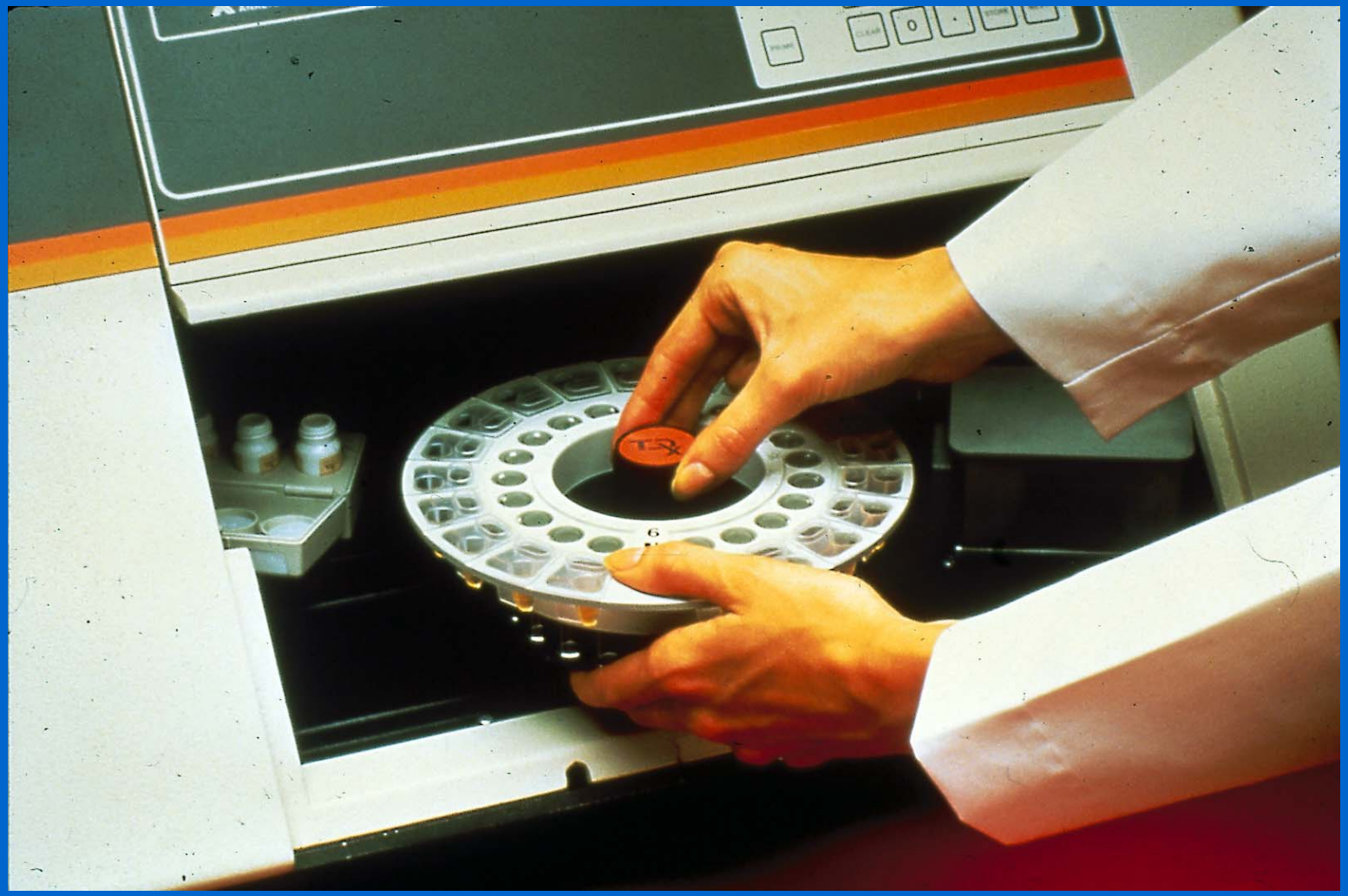
GAS LIQUID CHROMATOGRAPHY

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

FLUORESCENCE POLARIZATION IMMUNOASSAY



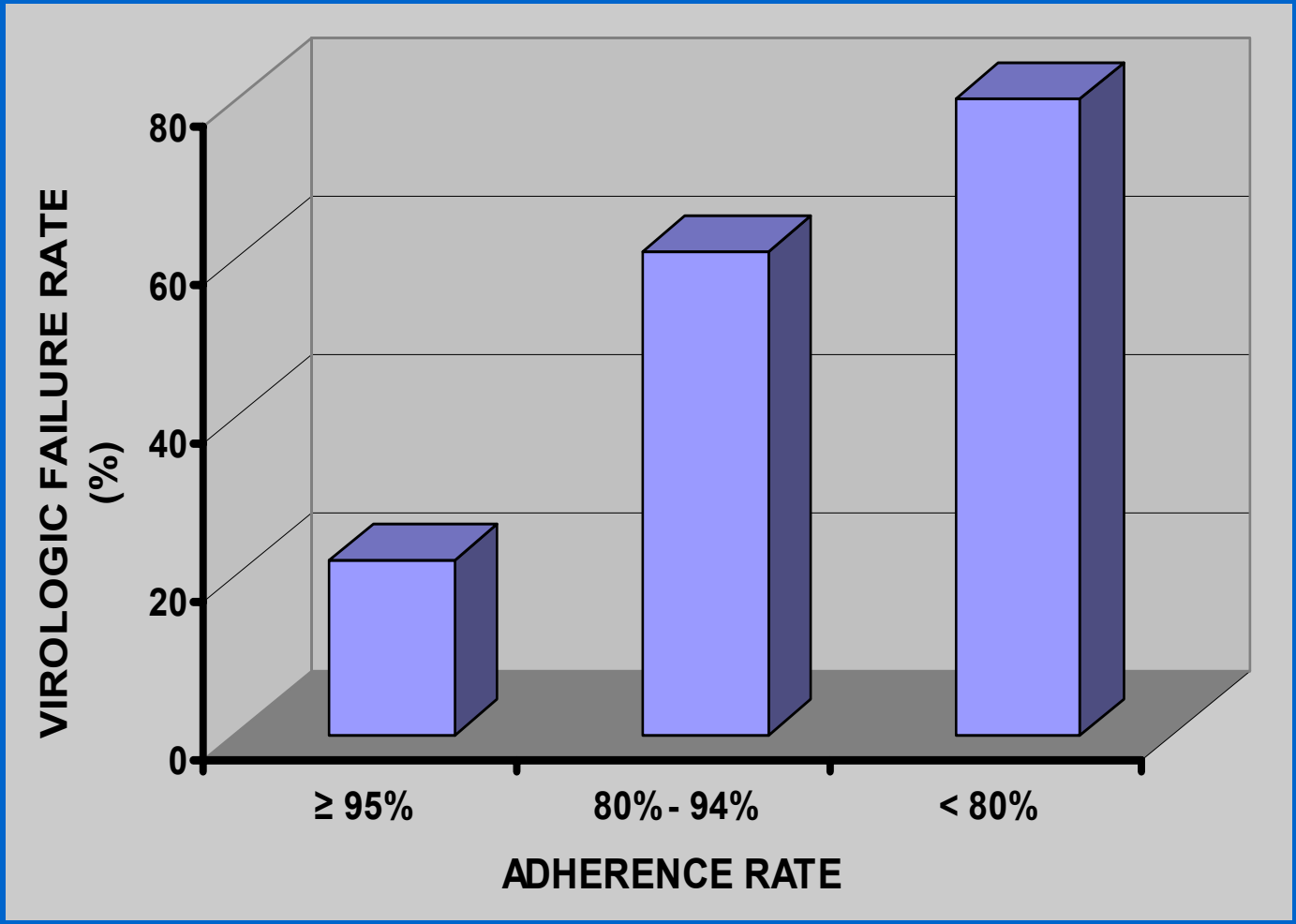
FLUORESCENCE POLARIZATION IMMUNOASSAY



DRUG CANDIDATES FOR TDM

- LOW THERAPEUTIC INDEX
- NO PHYSIOLOGIC OR THERAPEUTIC ENDPOINTS TO GUIDE DOSAGE
- PHARMACOKINETICS VARY WIDELY BETWEEN INDIVIDUALS
- NEED TO MONITOR ADHERENCE ?

EFFECT OF ADHERENCE RATE ON OUTCOME IN HIV INFECTED PATIENTS



From: Paterson DL, et al. Ann Intern Med 2000;133:21-30.

INDICATIONS FOR MEASURING BLOOD LEVELS

- TO EVALUATE SUSPECTED TOXICITY
- TO EVALUATE LACK OF THERAPEUTIC EFFICACY
- TO MONITOR PROPHYLACTIC THERAPY
- TO GUIDE DOSE ADJUSTMENT

TARGET CONCENTRATON STRATEGY

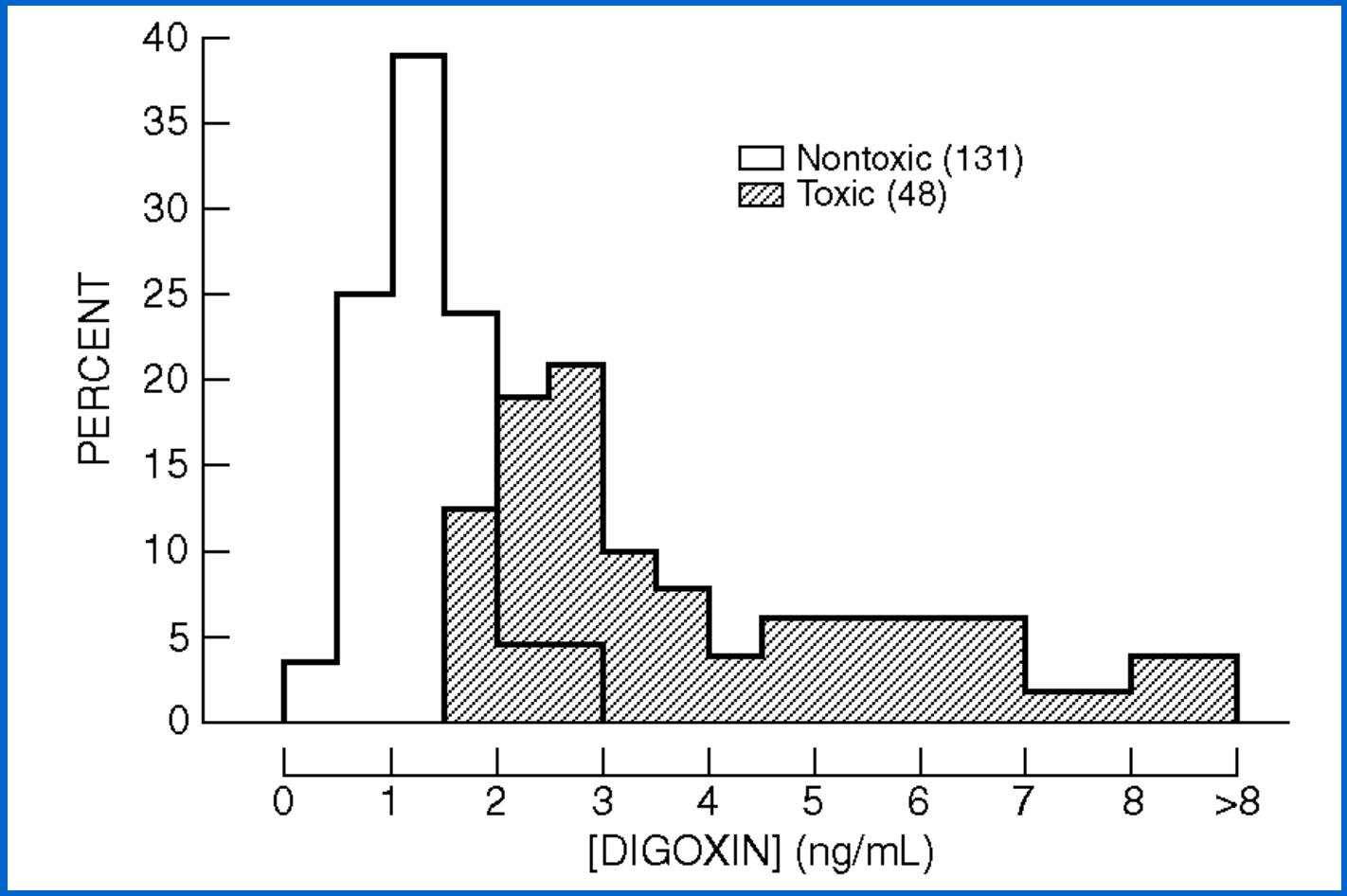
ESTIMATE INITIAL DOSE

TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

DIGOXIN LEVELS IN TOXIC AND NONTOXIC PATIENTS*



* From Smith TW and Haber E. J Clin Invest 1970;49:2377-86.

FACTORS INFLUENCING OUTCOME IN "GREY ZONE"

↑ RISK OF TOXICITY IN PATIENTS WITH CORONARY HEART DISEASE

↓ ECG EVIDENCE OF TOXICITY IF CONCURRENT THERAPY WITH ANTIARRHYTHMIC DRUGS

GUIDELINES FOR DIGOXIN LEVELS

USUAL THERAPEUTIC RANGE: **0.8 - 1.6 ng/ml**

POSSIBLY TOXIC LEVELS: **1.6 - 3.0 ng/ml**

PROBABLY TOXIC LEVELS: **> 3.0 ng/ml**

DIGOXIN TOXICITY IN TWO HOSPITALS*

	MGH	PBBH
DIGOXIN LEVELS:	40%	14%
MEAN DIGOXIN LEVEL (ng/mL):	0.98	1.82
DIGOXIN ADR RATE:	4%	10%
RISK ADJUSTED ADR RATE:	4.4%	9.3%

* Duhme DW, et al. Ann Intern Med 1974;80:516-9.

DIGOXIN CASE HISTORY

A 39 year-old man with mitral stenosis was hospitalized for mitral valve replacement. He had a history of chronic renal failure resulting from interstitial nephritis and was maintained on hemodialysis. His mitral valve was replaced with a prosthesis and digoxin therapy was initiated postoperatively in a dose 0.25 mg/day.

DIGOXIN CASE HISTORY (cont.)

Two weeks later, he was noted to be unusually restless in the evening. The following day, he died shortly after he received his morning digoxin dose. Blood was obtained during an unsuccessful resuscitation attempt, and the measured plasma digoxin concentration was 6.9 ng/mL.

TARGET CONCENTRATON STRATEGY

ESTIMATE INITIAL DOSE

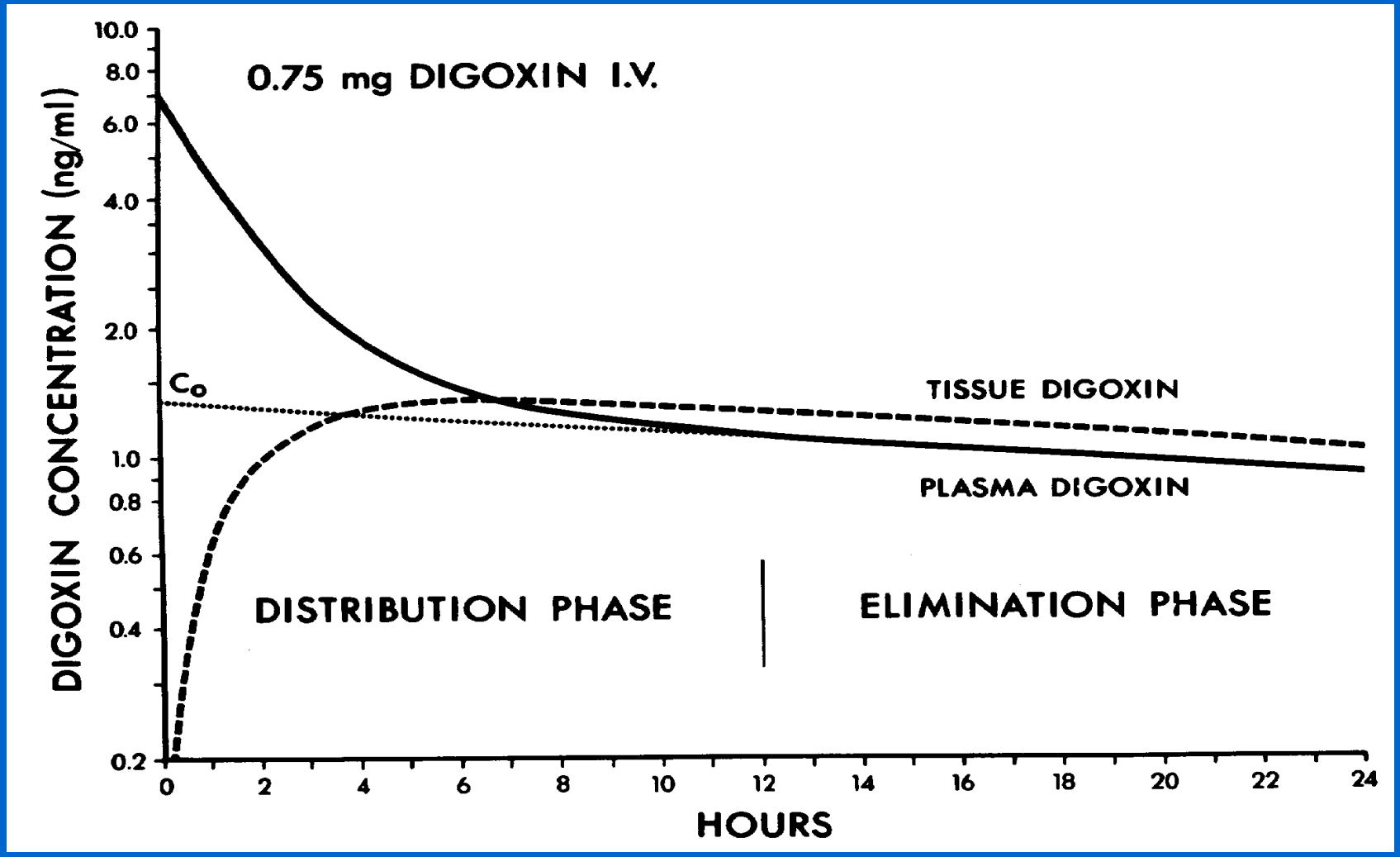
TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

BASED ON CONCEPT OF DISTRIBUTION VOLUME

DIGOXIN LEVELS AFTER IV DOSE

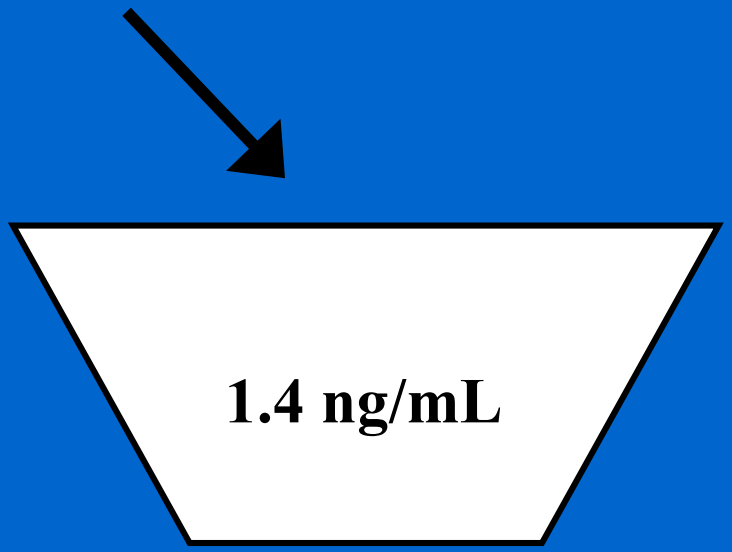


INITIAL DIGITALIZATION

DIGITALIZING DOSE

0.75 mg = 750 x 10^3 ng

$$V_d = \frac{750 \times 10^3 \text{ ng}}{1.4 \text{ ng/mL}} = 536 \text{ L}$$



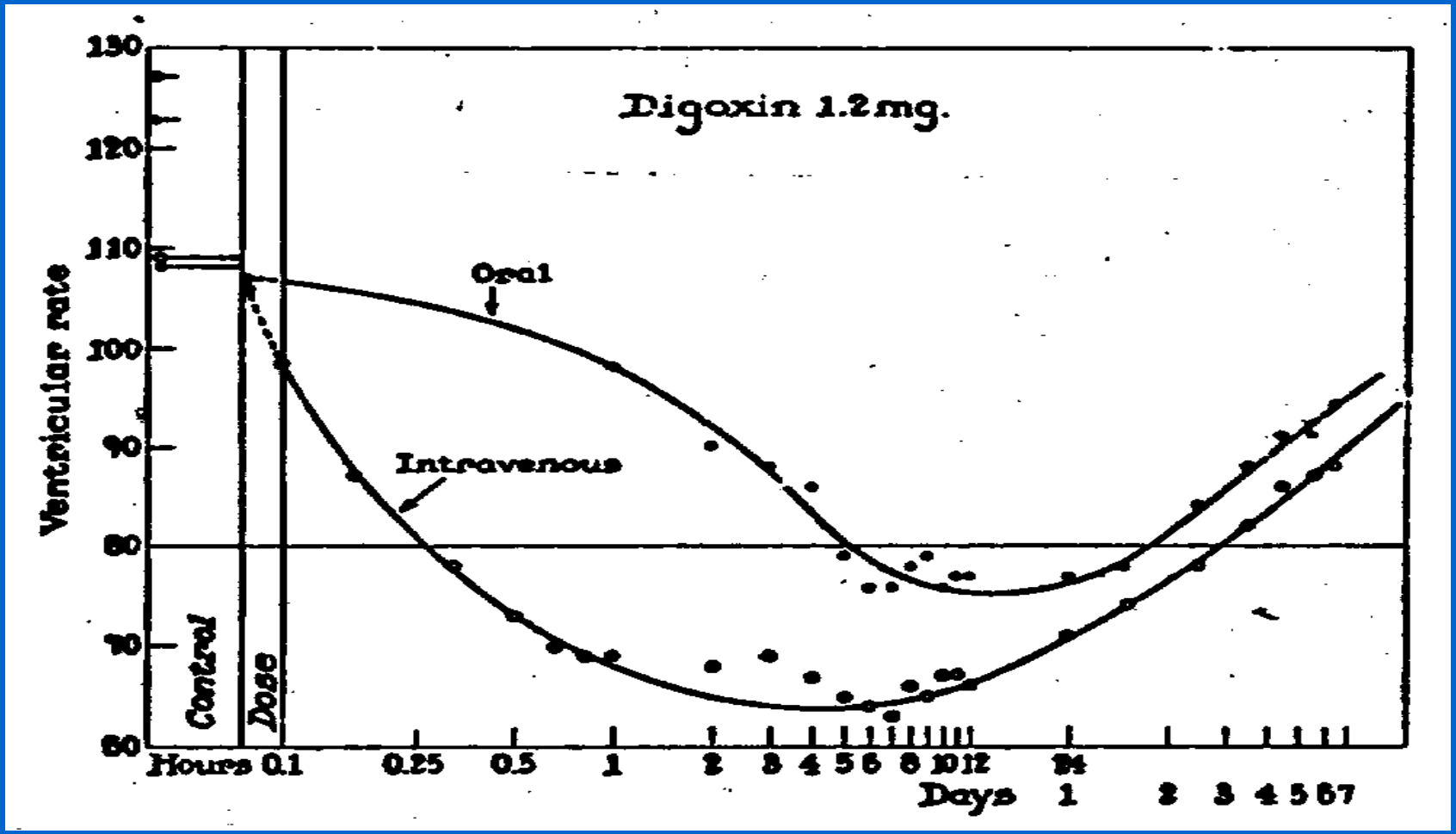
3 DISTRIBUTION VOLUMES

$$V_{d\,(extrap.)} = DOSE / C_0$$

$$V_{d\,(area)} = \frac{t_{1/2} \bullet CL_E}{0.693}$$

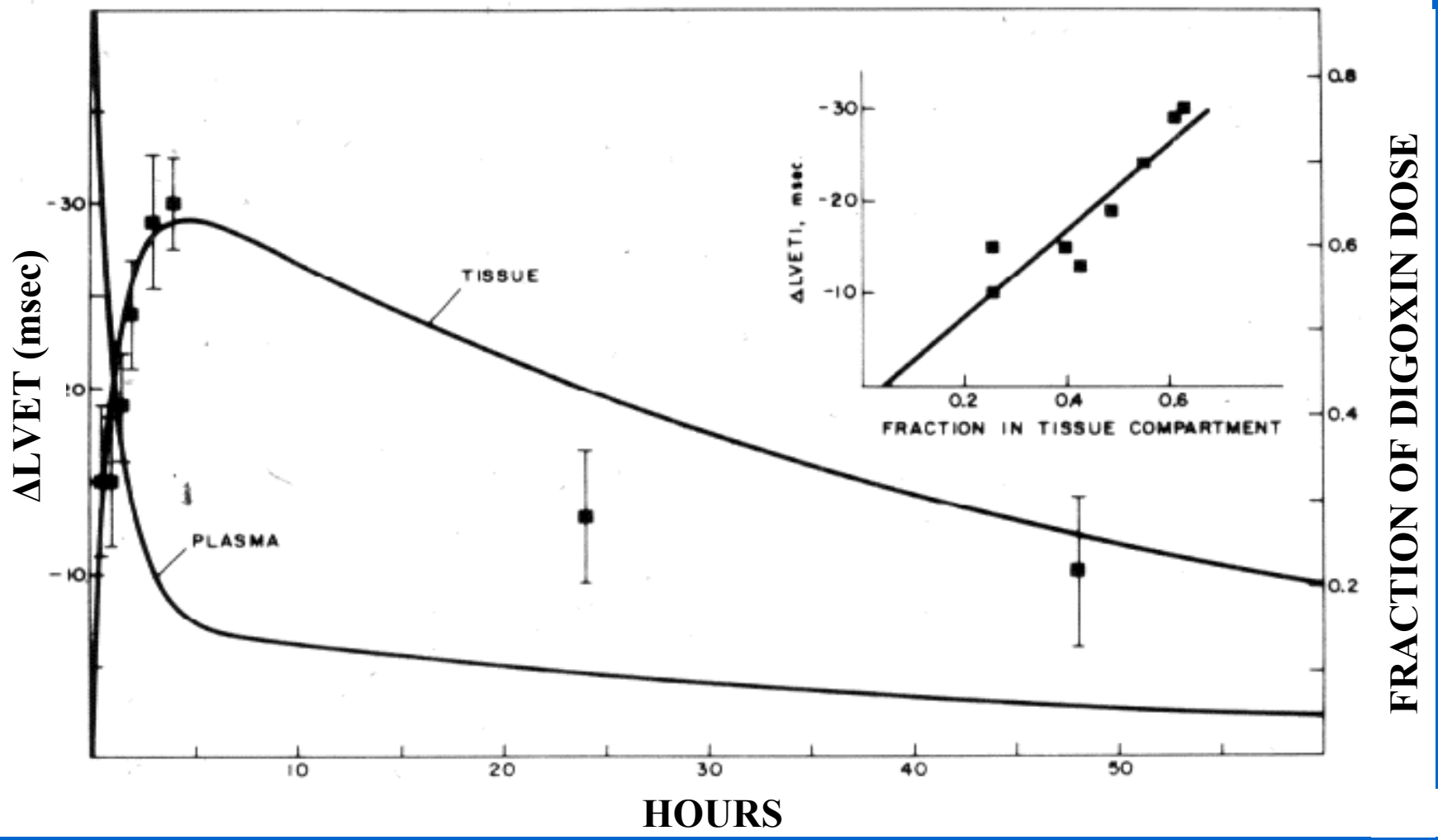
$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

DISTRIBUTION DELAYS ONSET OF DIGOXIN CHRONOTROPIC ACTION*

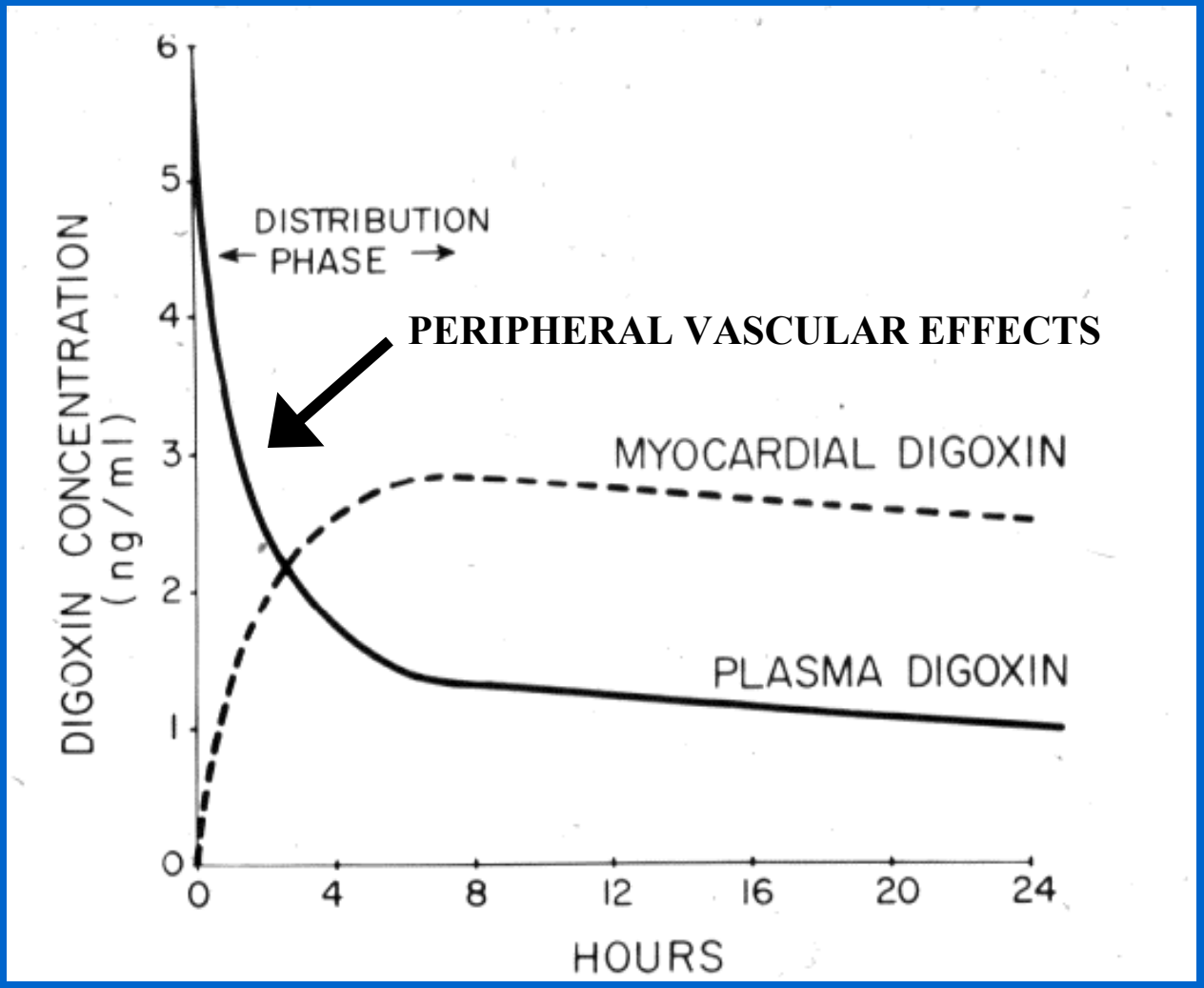


* From Gold H, et al. J Pharmacol Exp Ther 1953;109:45-57.

DISTRIBUTION DELAYS ONSET OF DIGOXIN INOTROPIC ACTION*



PLASMA VS. MYOCARDIAL DIGOXIN LEVELS



TARGET CONCENTRATON STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL

LOADING DOSE

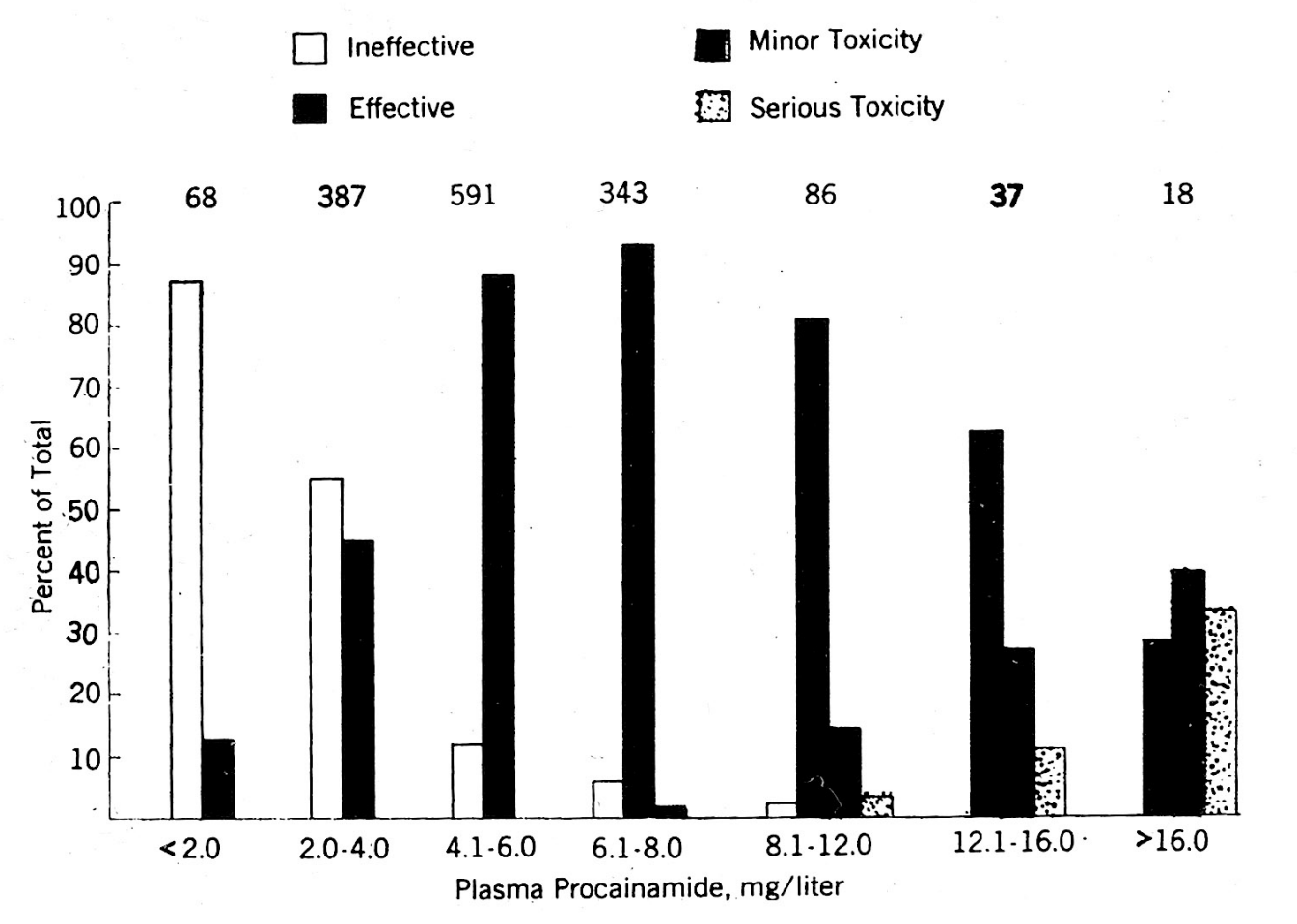
MAINTENANCE DOSE

BASED ON CONCEPTS OF ELIMINATION HALF LIFE AND CLEARANCE

ELIMINATION HALF-LIFE

ELIMINATION HALF-LIFE IS THE TIME REQUIRED FOR THE PLASMA CONCENTRATION (OR TOTAL BODY STORES) OF A DRUG TO FALL TO HALF OF THE CONCENTRATION (OR AMOUNT) PRESENT AT SOME PREVIOUS TIME.

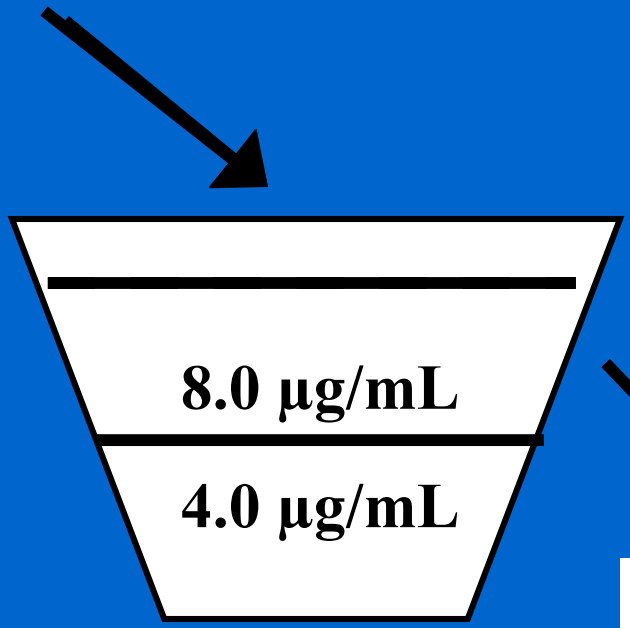
CORRELATION OF PA LEVELS WITH EFFECT*



* From Koch-Weser J, Klein SW. JAMA 1971;215:1454-60.

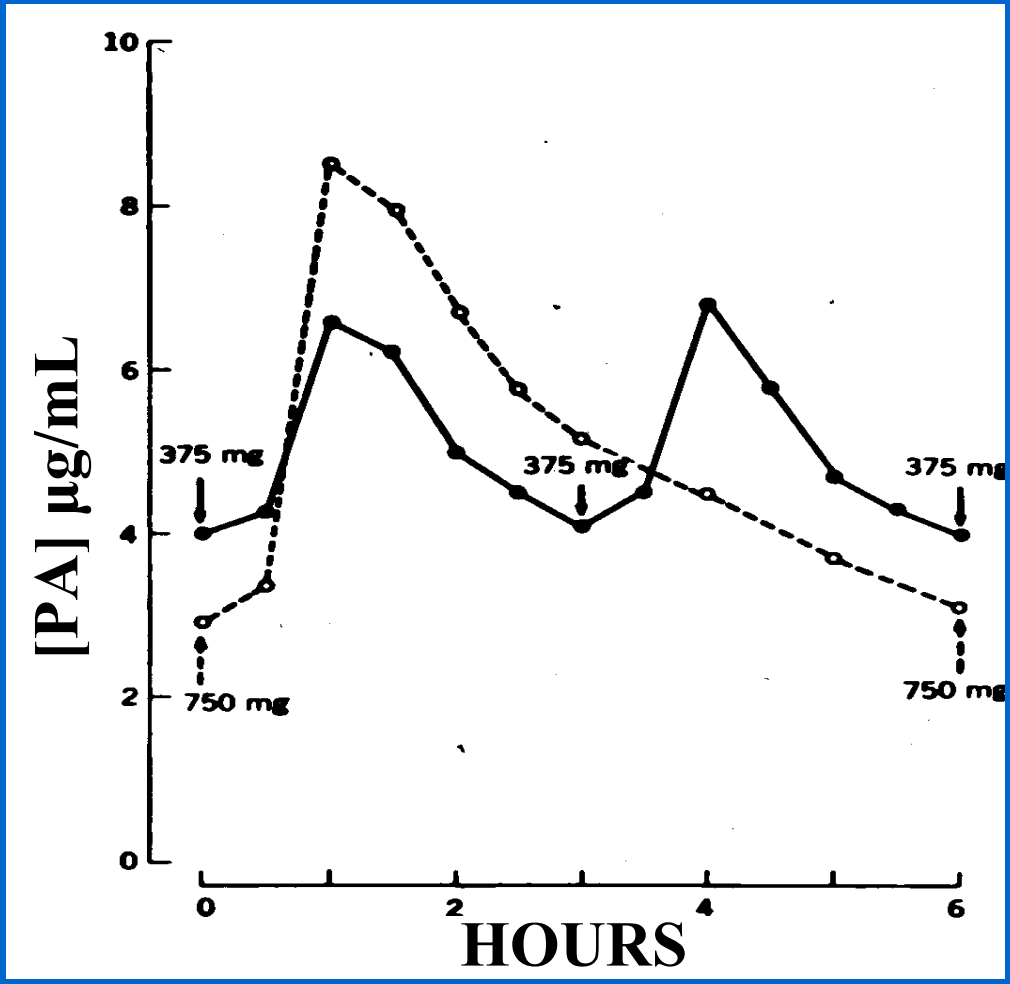
MAINTENANCE DOSE EVERY HALF-LIFE

MAINTENANCE DOSE
500 mg = ½ Loading Dose



500 mg lost after 1 half-life

BASIS FOR RECOMMENDING PA DOSING EVERY 3 HOURS*



* From Koch-Weser J, Klein SW. JAMA 1971;215:1454-60.

Parke-Davis introduces

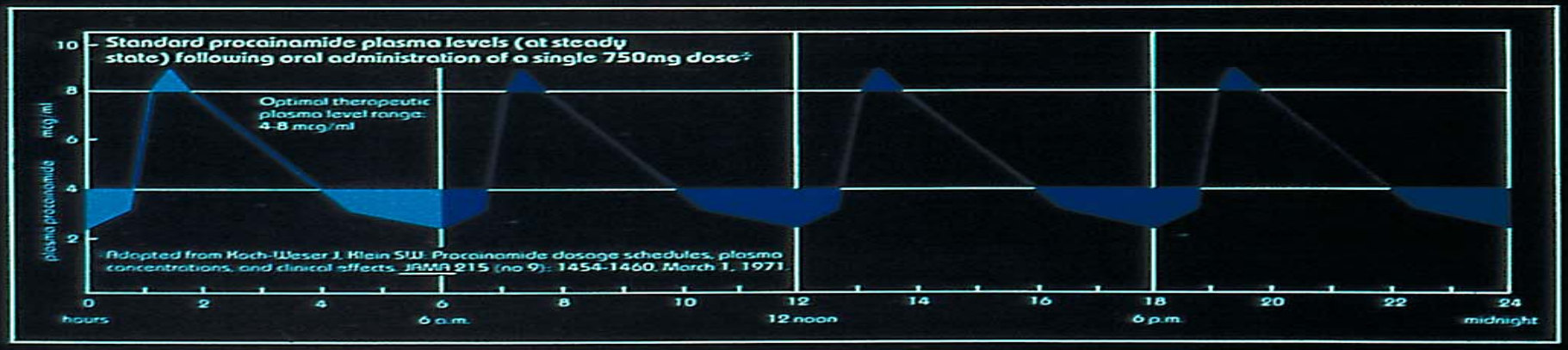
SUSTAINED RELEASE

new Procan™ SR

(PROCAINAMIDE HYDROCHLORIDE TABLETS)

a therapeutic gap exists when conventional oral procainamide therapy is administered at greater than 3 hour intervals

- Adequate blood levels maintained only 2/3 of the time during a 6 hour dosing interval
- Patient control may be threatened



"To avoid unacceptable fluctuations in the plasma levels of procainamide, the oral preparation available at present has to be given at 3 h intervals . . . ."[1]

CONVENTIONAL VS. SR PROCAINAMIDE*

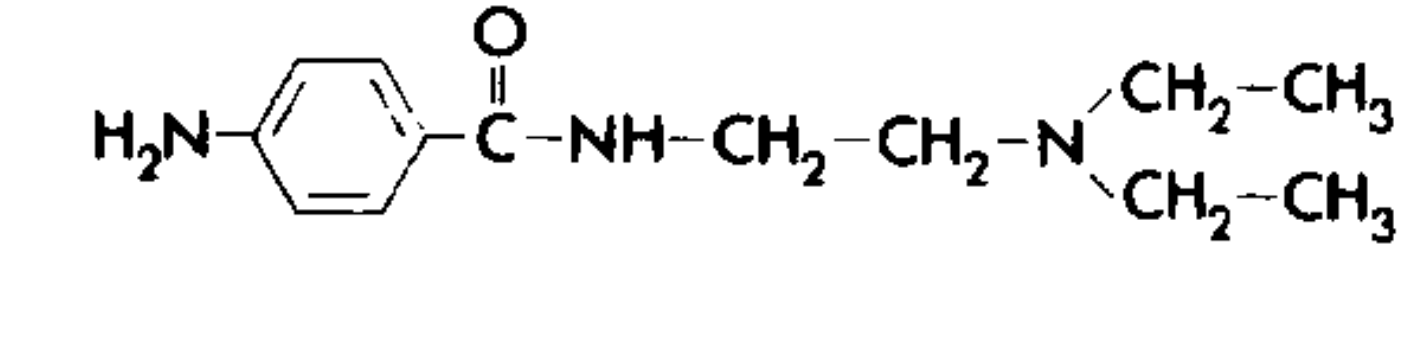
	CONVENTIONAL FORMULATION	PROCAN SR©
$t_{1/2}$ (hr):	3.09	4.34
DOSE INTERVAL (hr):	3	6

* Smith TC, Kinkel AW. Curr Ther Res 1980;27:217-28.

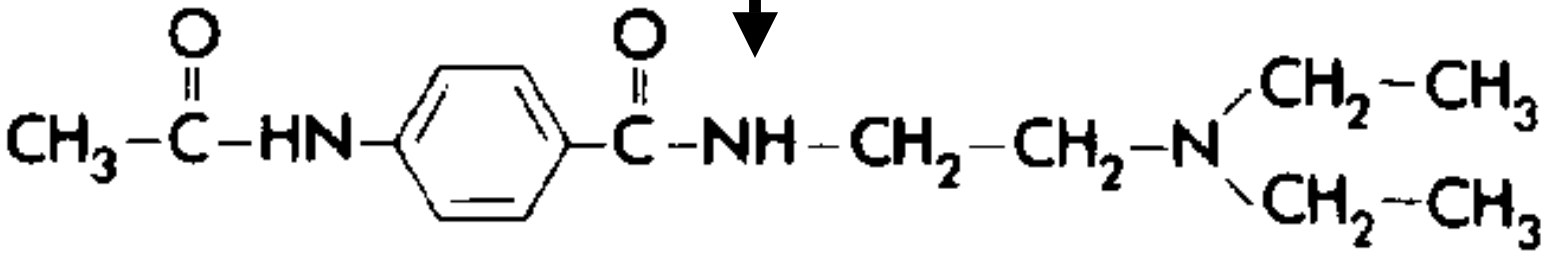
WHY IS 6 HR DOSING EFFECTIVE?

FORMULATION	$T_{1/2}$	DOSE FREQUENCY
IMMEDIATE RELEASE	3.0 hr	6 hr
PROCAN SR©	4.3 hr	6 hr

PROCAINAMIDE ACETYLATION



PROCAINAMIDE



N-ACETYLPROCAINAMIDE (NAPA)

TARGET CONCENTRATON STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

⇩

BEGIN THERAPY

⇩

ASSESS THERAPY

PATIENT RESPONSE

DRUG LEVEL

⇩

REFINE DOSE ESTIMATE

⇩

ADJUST DOSE

MAINTENANCE DIGOXIN THERAPY

MAINTENANCE DOSE
0.25 mg

NORMAL DAILY LOSS:
= 1/3 Total Body Stores
= 1/3 (0.75) mg
= 0.25 mg

DAILY LOSS
0.25 mg

DIGOXIN CUMULATION

.25 x 2/3 = .17 DOSE #1

+.25 DOSE #2

.42 x 2/3 = .28

+.25 DOSE #3

.53 x 2/3 = .36

+.25 DOSE #4

.61 x 2/3 = .41

+.25 DOSE #5

.66 x 2/3 = .44

+.25 DOSE #6

.69 x 2/3 = .46

+.25 DOSE #7

.71

CUMULATION FACTOR

$$CF = \frac{1}{\left(1 - e^{-k\tau}\right)}$$

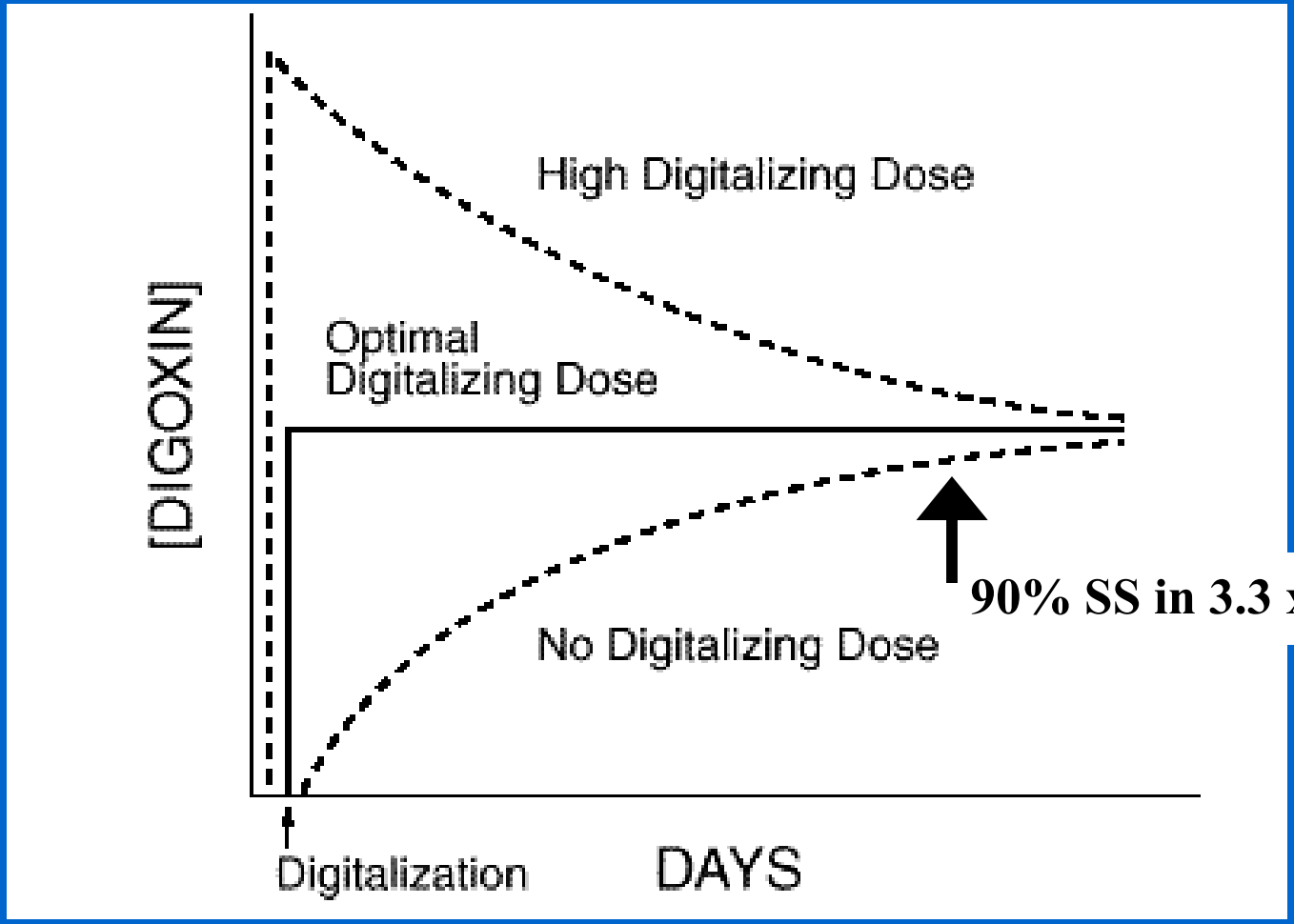
τ is dose interval

k is elimination rate constant

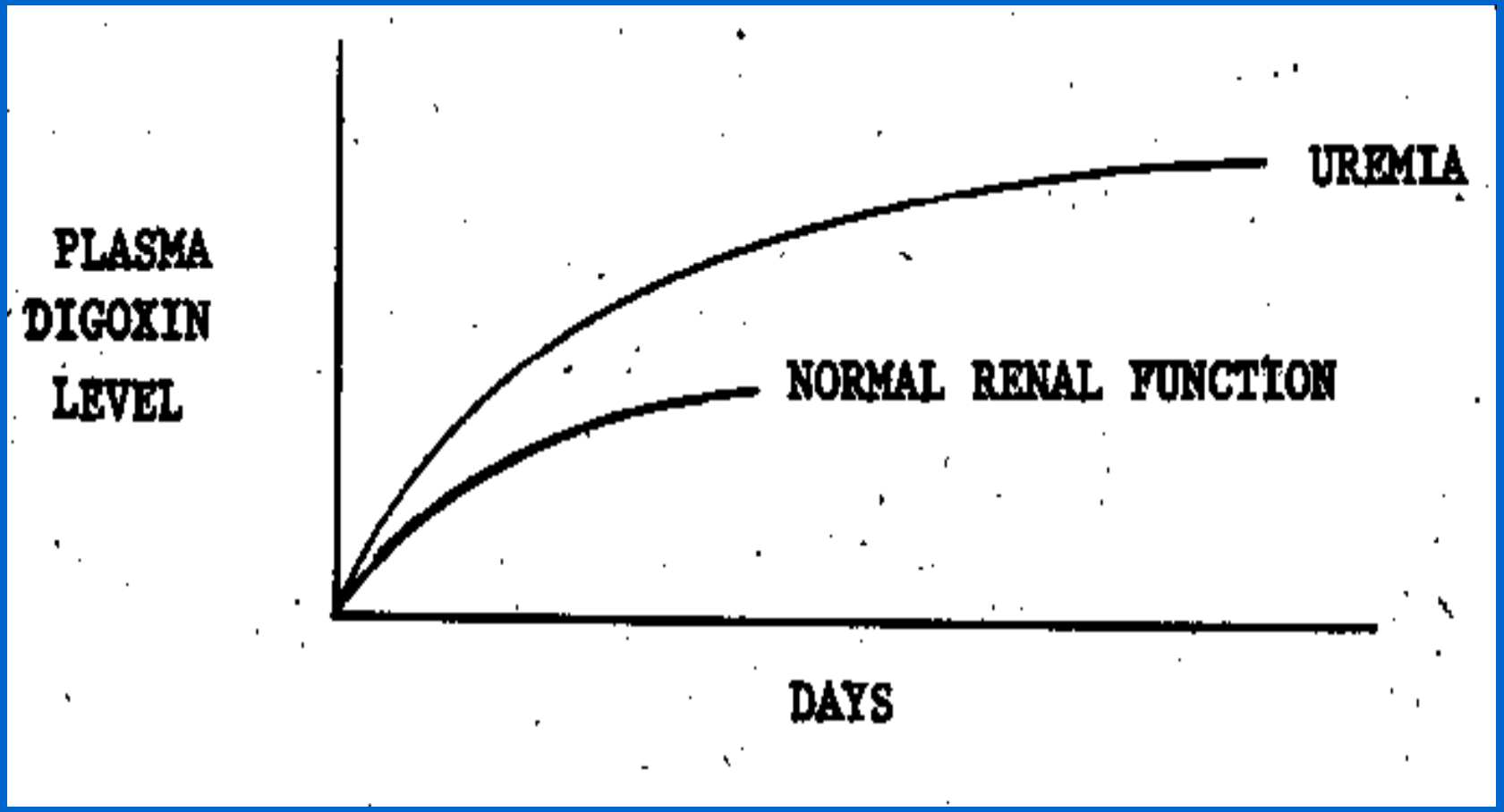
ELIMINATION RATE CONSTANT

$$k = \frac{0.693}{t_{1/2}}$$

LOADING & MAINTENANCE DOSES



TIME-COURSE OF DIGOXIN CUMULATION



STEADY STATE CONCENTRATION

CONTINUOUS INFUSION:

$$C_{SS} = \frac{I}{CL_E}$$

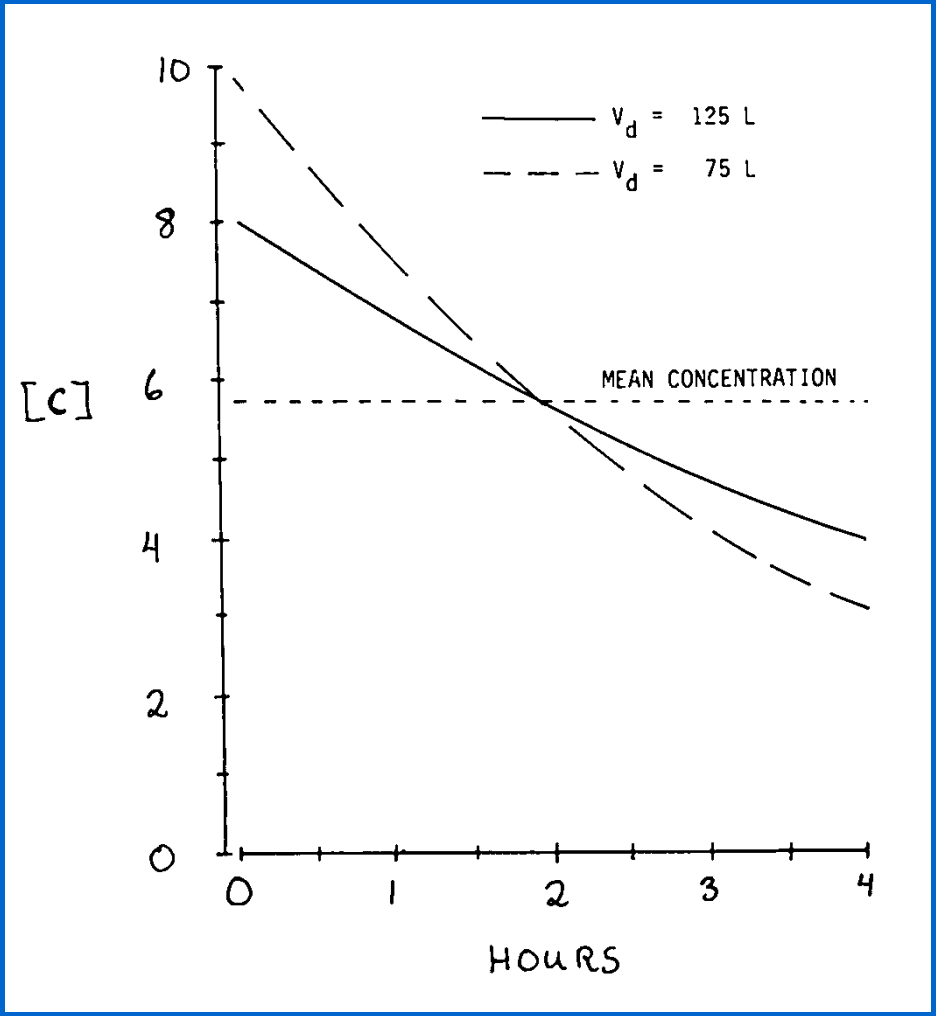
INTERMITTENT DOSING:

$$\overline{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

STEADY STATE CONCENTRATION

- NOT DETERMINED BY LOADING DOSE
- NOT DETERMINED BY V_d

V_d AFFECTS PEAK AND TROUGH BUT *NOT* MEAN LEVELS



STEADY STATE CONCENTRATION

CONTINUOUS INFUSION:

$$C_{SS} = \frac{I}{CL_E}$$

INTERMITTENT DOSING:

$$\overline{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

STEADY STATE CONCENTRATION

- NOT DETERMINED BY LOADING DOSE
- NOT DETERMINED BY V_d
- CHANGES IN MAINTENANCE DOSE RESULT IN DIRECTLY PROPORTIONAL CHANGES IN C_{SS} FOR MOST DRUGS

TARGET CONCENTRATON STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

⇩

BEGIN THERAPY

⇩

ASSESS THERAPY

PATIENT RESPONSE
DRUG LEVEL

⇩

REFINE DOSE ESTIMATE

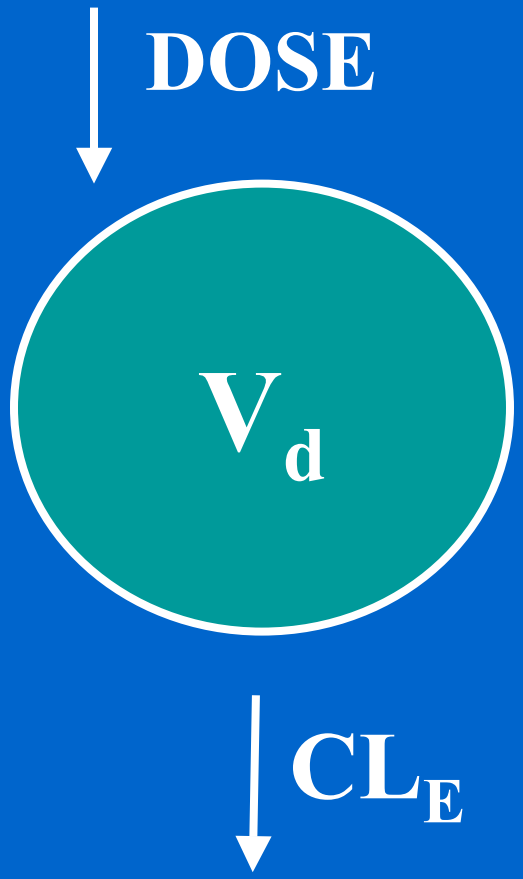
⇩

ADJUST DOSE

PHARMACOKINETIC MODELS

WHAT PHARMACOKINETIC PARAMETERS ARE PRIMARY?

SINGLE COMPARTMENT MODEL



ELIMINATION HALF-LIFE

$$t_{1/2} = \frac{0.693 \bullet V_{d(area)}}{CL_E}$$

THEREFORE, $t_{1/2}$ IS NOT A PRIMARY PHARMACOKINETIC PARAMETER

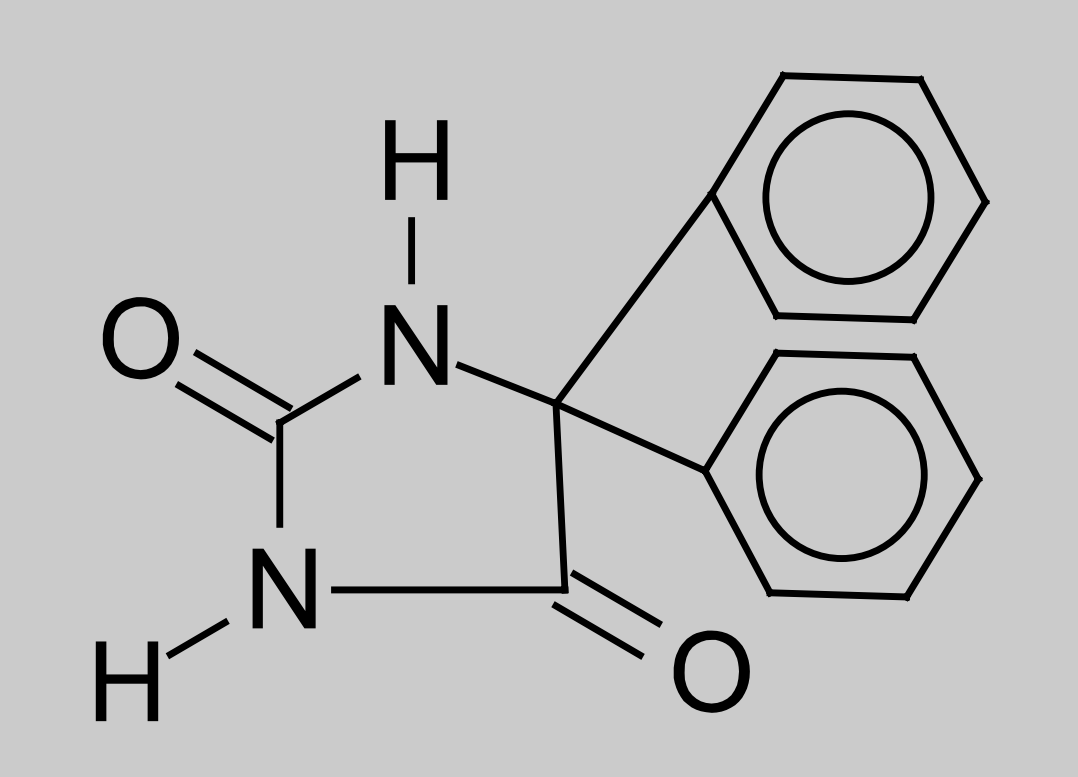
3 DISTRIBUTION VOLUMES

$$V_{d\,(extrap.)} = DOSE \,/\, C_0$$

$$V_{d\,(area)} = \frac{t_{1/2} \cdot CL}{0.693}$$

$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

SOME DRUGS NOT ELIMINATED BY FIRST ORDER KINETICS



PHENYTOIN (DILANTIN)

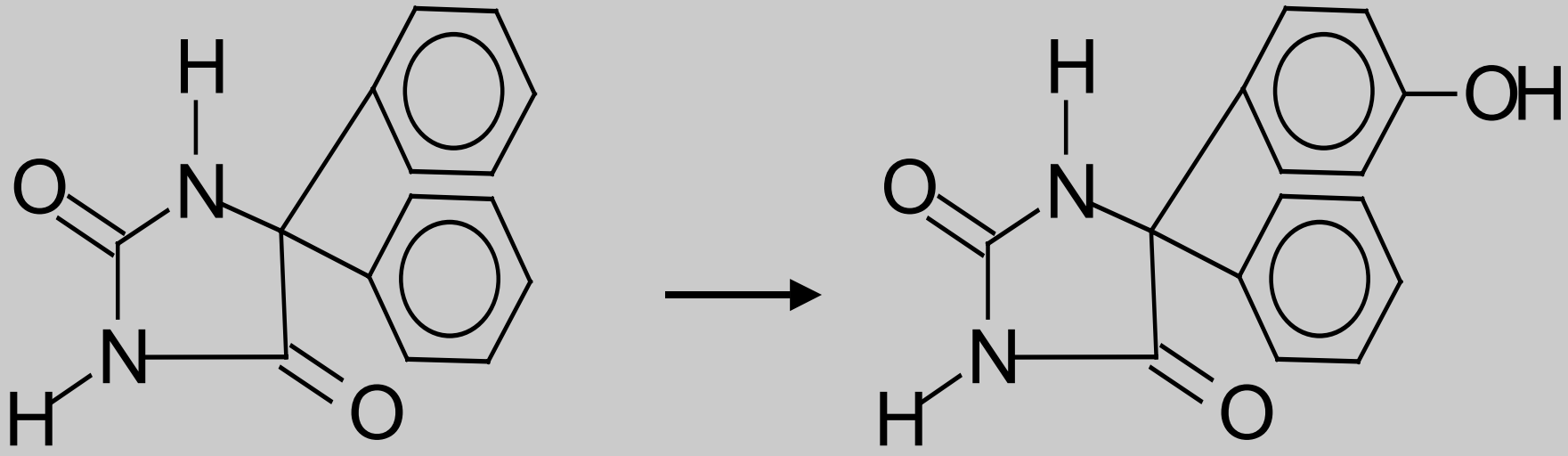
NONCANCER DRUGS CAUSING ADR'S*

PHENYTOIN**	CARBAMAZEPINE**
PREDNISONE	CODEINE
DIGOXIN**	LITHIUM**
AMIODARONE	THEOPHYLLINE**
ASPIRIN**	DESIPRAMINE**
CO-TRIMOXAZOLE	DEXAMETHASONE
PENTAMIDINE	GENTAMICIN**

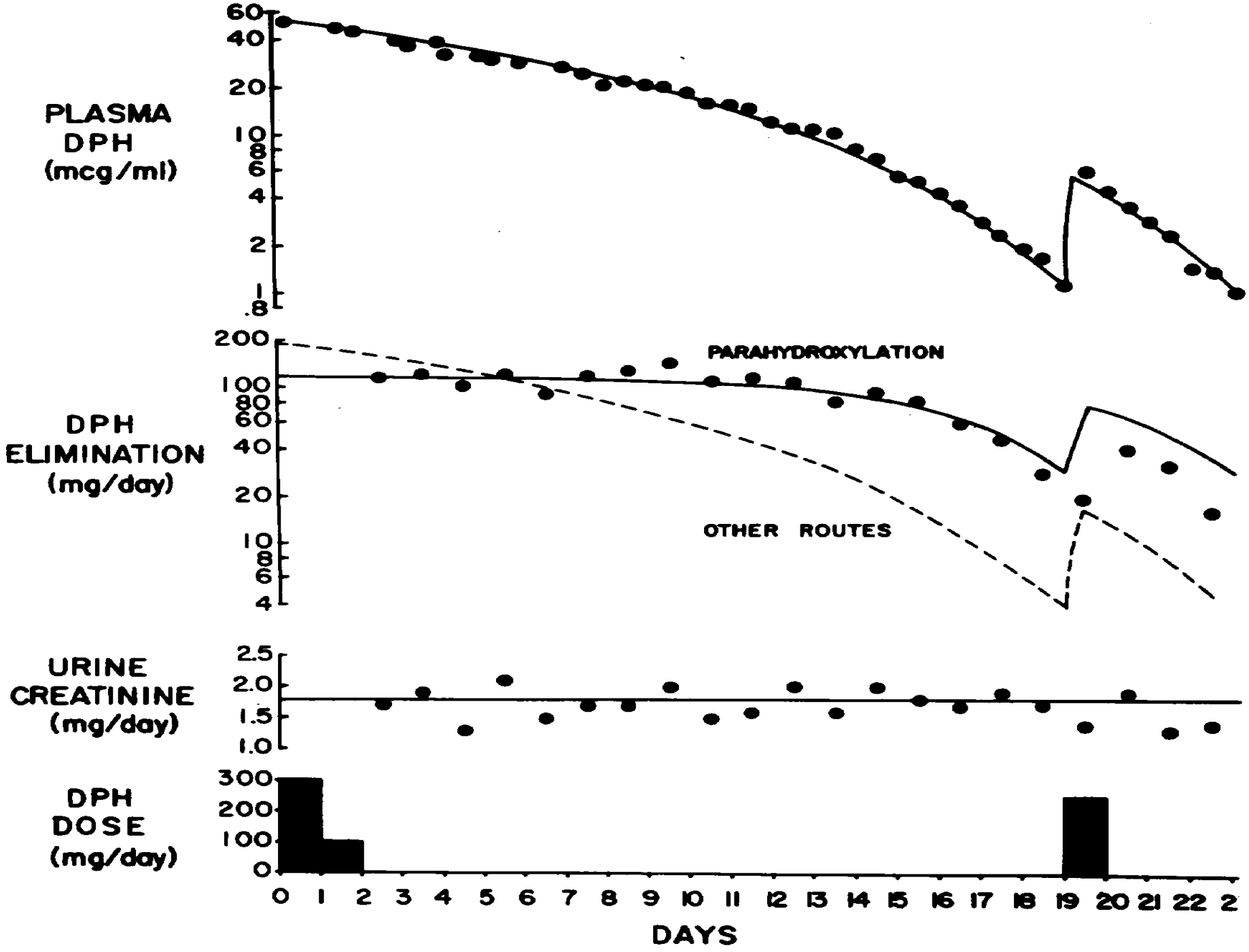
* 1988 NMH DATA (CLIN PHARMACOL THER 1996;60:363-7)

** DRUGS FOR WHICH PLASMA LEVELS ARE AVAILABLE

PHENYTOIN HYDROXYLATION



PHENYTOIN ***p*-HPPH**


PLASMA DPH (mcg/ml)
60
40
20
10
8
6
4
2
1
.8
DPH ELIMINATION (mg/day)
200
100
80
60
40
20
10
8
6
4
PARAHYDROXYLATION
OTHER ROUTES
URINE CREATININE (mg/day)
2.5
2.0
1.5
1.0
DPH DOSE (mg/day)
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 2
DAYS

STEADY STATE EQUATIONS

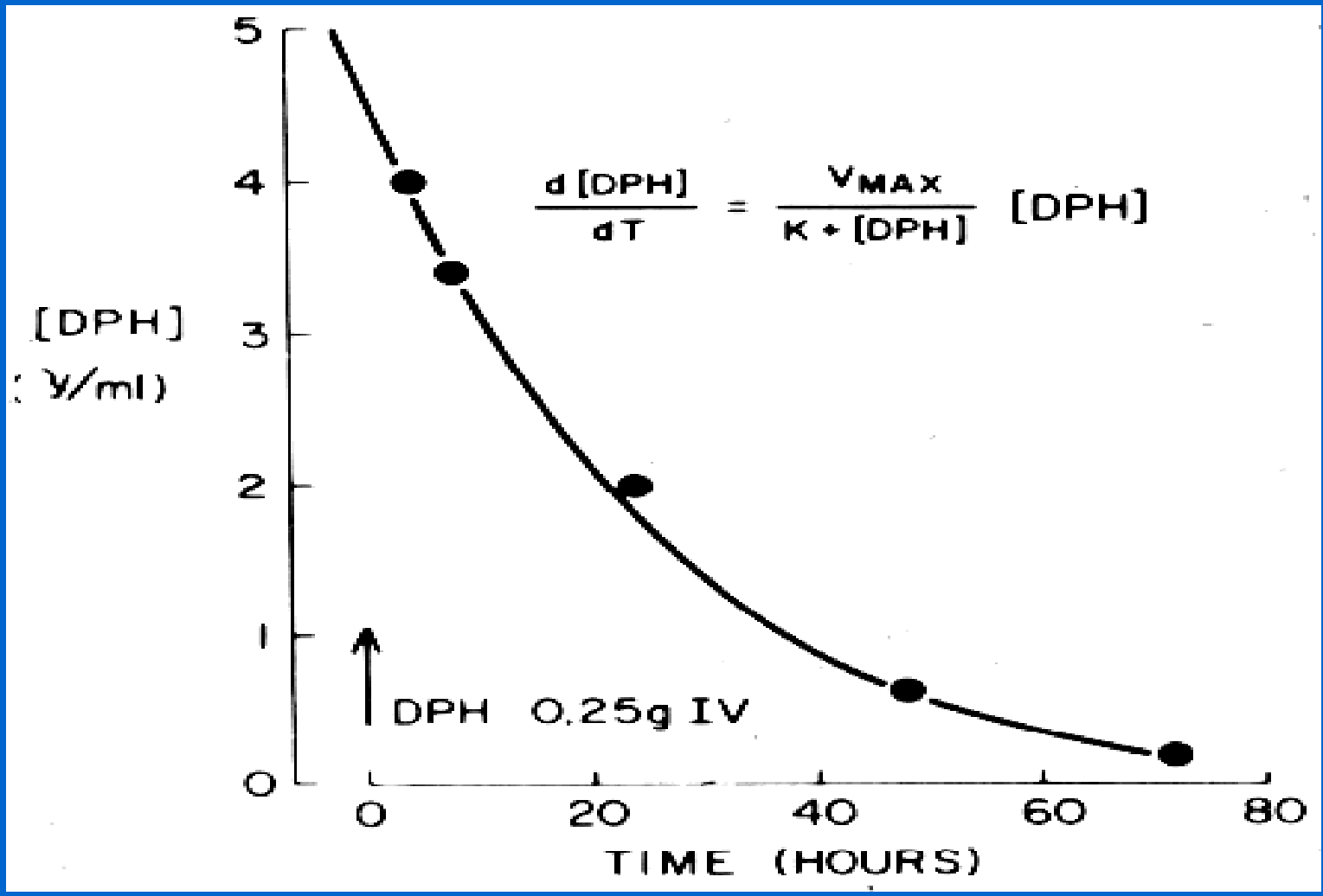
FIRST ORDER KINETICS

$$\text{DOSE}/\tau = CL_E \bullet \overline{C}_{SS}$$

MICHAELIS - MENTEN KINETICS

$$\text{DOSE}/\tau = \left[\frac{V_{max}}{K_m + \overline{C}_{SS}} \right] \overline{C}_{SS}$$

PHENYTOIN KINETICS IN NORMAL SUBJECTS

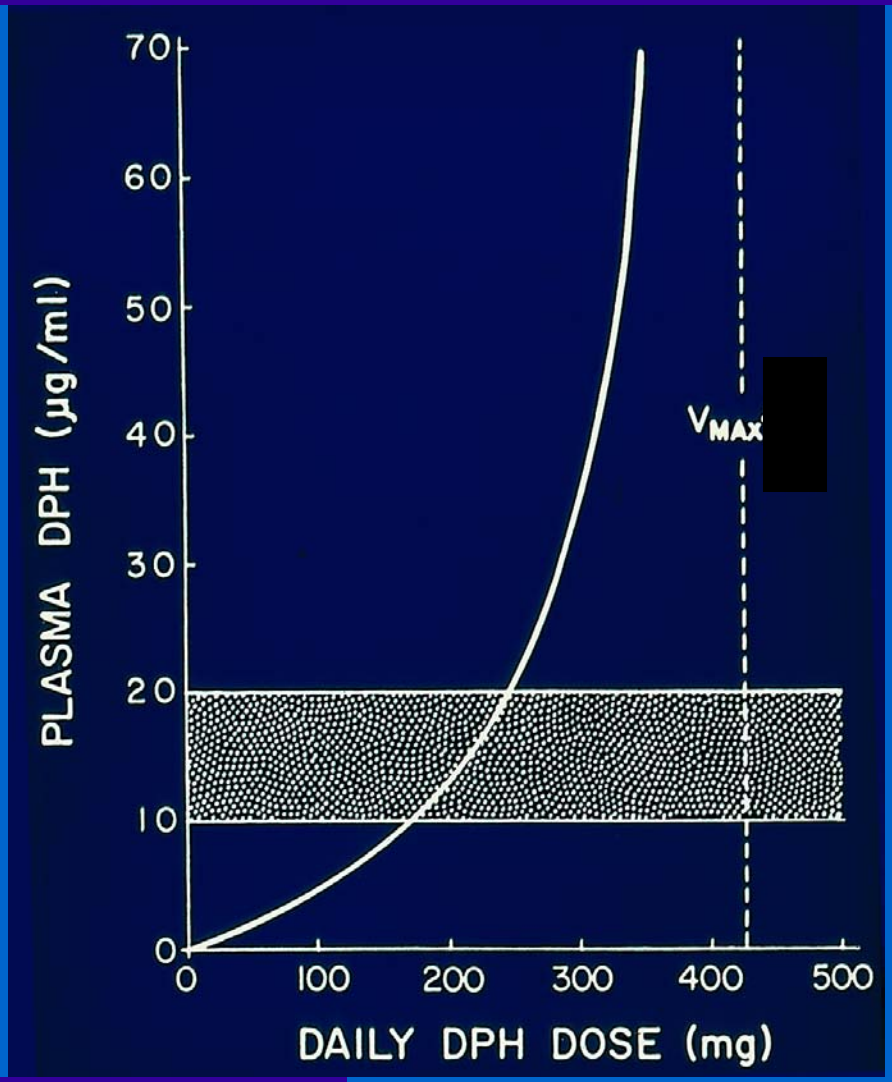


RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

PHENYTOIN DOSE (mg/day)	PLASMA LEVEL µg/mL
300	10
400	20
500	30

* From: Kutt H, McDowell F: J Am Med Assoc 1968;203:969-72.

PATIENT WHO BECAME TOXIC ON A PHENYTOIN DOSE OF 300 mg/day



PHENYTOIN CASE HISTORY

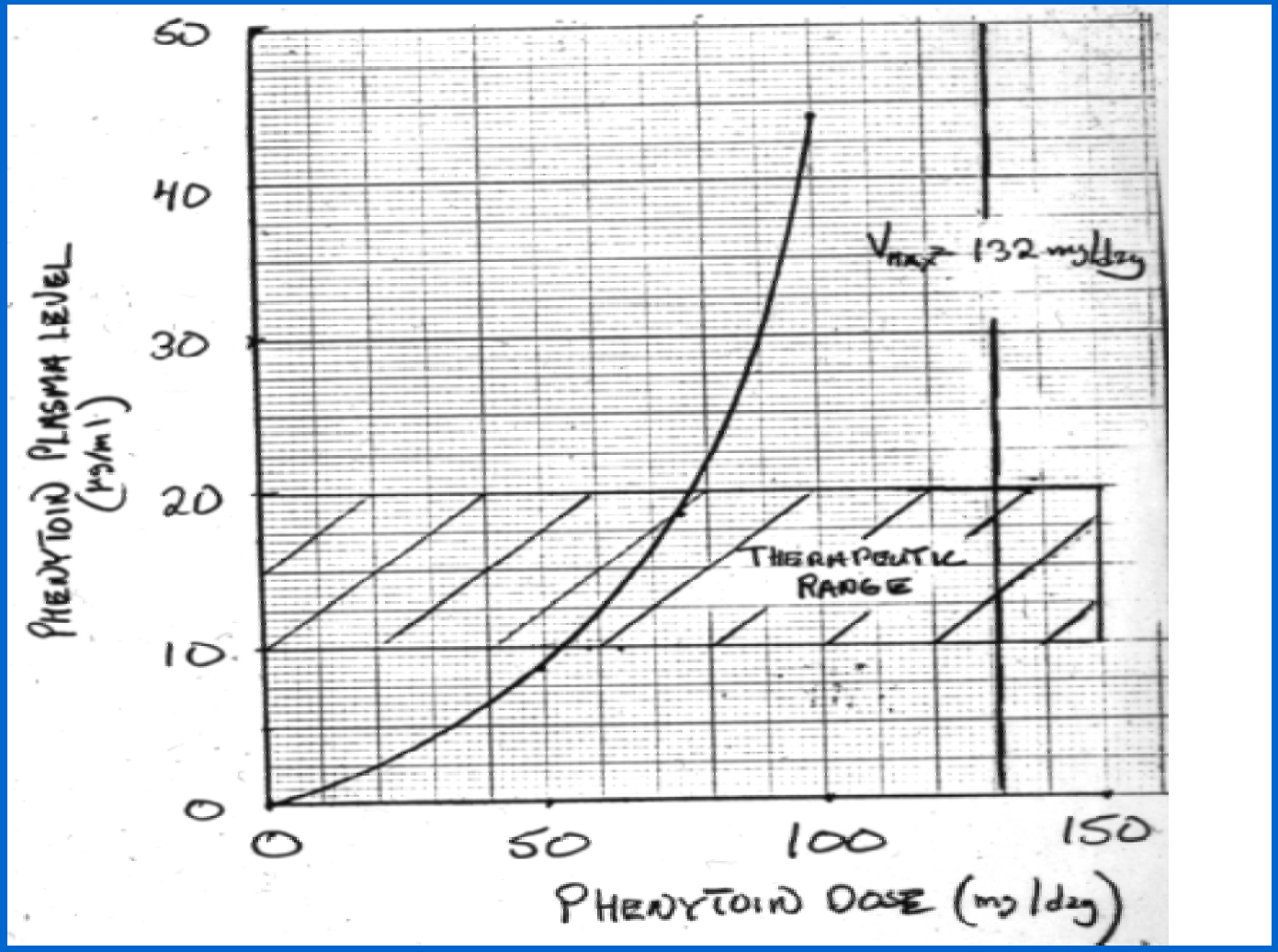
After inpatient evaluation for a generalized seizure, a 28-year-old woman was discharged on phenytoin therapy at a dose of 300 mg/day.

After 5 days of therapy, she presented to the hospital's emergency department with marked ataxia. Her phenytoin plasma concentration was found to be 27 µg/mL. She was sent home on a reduced phenytoin dose of 200 mg/day.

PHENYTOIN CASE HISTORY (cont.)

Two days later, she returned to the emergency department with more severe ataxia. Her phenytoin plasma concentration was now 32 μg/mL. Non-compliance was suspected but a clinical pharmacology evaluation was requested.

PATIENT WITH VERY LOW V_{MAX}



BASIS OF APPARENT FIRST-ORDER KINETICS

$$\frac{dC}{dt} = \left[\frac{V_{max}}{K_m + C} \right] C$$

If $K_m > C$:

$$\frac{dC}{dt} = \left[\frac{V_{max}}{K_m} \right] C = \text{"k"}\, C$$

CONCLUDING THOUGHTS

- EQUATIONS DERIVED IN "PRINCIPLES OF CLINICAL PHARMACOLOGY TEXTBOOK"
- LAPLACE TRANSFORMS INTRODUCED WITH TABLES IN APPENDIX I
- PRACTICE PROBLEMS AT END OF CHAPTER 2 WITH ANSWERS IN APPENDIX II